REMARKS

The Official Action of July 24, 2007, and the prior art relied upon therein have been carefully reviewed. The claims in the application are now claims 1-14, 21-33, 42 and 43, and these claims define patentable subject matter warranting their allowance. Accordingly, the applicants respectfully request favorable reconsideration and allowance.

Acknowledgement by the PTO of the receipt of applicants' papers filed under Section 119 is noted.

Claims 1 and 2 have been allowed, and applicants understand that these claims are deemed by the PTO to define novel and unobvious subject matter under Sections 102 and 103. Similarly, claims 5, 6, 10, 13 and 14 have only been objected to as being dependent on a rejected base claim, but are otherwise indicated as being directed to allowable subject matter; again, applicant understands that these claims also are deemed by the PTO to define novel and unobvious subject matter under Sections 102 and 103.

The clerical or typographical errors helpfully pointed out by the examiner in claims 11, 12, 29 and 30 have now been corrected. However, for the record, such minor

errors do not rise to the level of requiring a rejection based on the second paragraph of Section 112, and the amendments to correct the errors are not substantial amendments relating to patentability. No limitations have been added and none are intended; the scope of the claims remains the same.

Claims 15-43 have been rejected under the first paragraph of Section 112. The rejection is respectfully traversed.

First, claims 15-20 and 34-41 have been deleted without prejudice, so applicant need not address this rejection as regards those claims at the present time. Applicant respectfully reserves the right to pursue those claims and/or similar claims in a continuing application without any penalty whatsoever, if applicant chooses to do so, in such a case relying on Sections 120 and 119.

According to the rejection, these "claims contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention".

Pending claims 21-33, 42 and 43 are directed to method for the treatment or prevention of diseases or disorders related to cell migration mediated by GAG-ECAM

interactions. Claims 21-33 are directed to methods for the treatment or prevention of diseases or disorders related to cell migration mediated by GAG-L-selectin interaction, particularly an inflammatory process claimed in claim 33, such method comprising administering a thieno[2,3-c]pyridine compound as now defined in amended claims 21-32.

Claims 42 and 43 are not amended. These claims are directed to a method for the treatment of inflammatory bowel disease and a method for the treatment of multiple sclerosis, respectively, comprising administration of compound 11. These claims are adequately enabled by the description, as explained below.

The background section of the present application describes the role of GAGs and selectins in diseases and disorders related to cell migration and cell-cell interactions, particularly inflammatory diseases. Thus, it is stated that the inflammatory response is mediated primarily by leukocytes, neutrophils and lymphocytes, which circulate in the blood and reversibly interact with the vascular endothelium. In response to inflammatory stimuli, the leukocytes adhere tightly to the vascular endothelium, migrate (extravasate) through the vessel wall, and subsequently move along a chemotactic gradient toward the inflammatory stimulus.

The interaction of leukocytes with vascular endothelial cells is thus an essential initial step in the inflammatory response.

Selectins play a key role in inflammation, as they are responsible for the initial attachment of blood borne leukocytes to the vasculature. Selectins are effector cell adhesion molecules, which regulate neutrophil and lymphocyte adhesion to and entry into lymphoid tissues and sites of inflammation. Preventing selectin-mediated cell adhesion can ameliorate or circumvent the deleterious consequences of inflammation. Therefore, selectins are the prime target for the therapy of cell-adhesion disorders, specifically for treatment of inflammation.

Selectins mediate their adhesive functions via lectin domains that bind to carbohydrate ligands. Emerging evidence indicates that GAGs, and in particular HS-GAGs, are carbohydrate receptors with which the selectins interact (see references supporting the interaction between GAGs and selectins listed on page 3, lines 26-29 of applicants' specification). Glycosaminoglycans (GAG or GAGs) are naturally-occurring carbohydrate-based molecules implicated in the regulation of a number of cellular processes, including blood coagulation, angiogenesis, tumor growth, and smooth

muscle cell proliferation, most likely by interaction with effector molecules. GAGs are often, but not always, found covalently bound to protein cores in structures called proteoglycans. Proteoglycan structures are abundant on cell surfaces and are associated with the extracellular matrix around cells.

The present application provides pharmaceutical compositions comprising small organic thieno[2,3-c]pyridine compounds for medical and diagnostic use, these thieno[2,3-c]pyridine compounds being inhibitors of the interactions between effector cell adhesion molecules (ECAMs), specifically L-selectin and P-selectin, with GAGs, specifically heparan sulfate glycosaminoglycans (HS-GAGs). Accordingly, these compositions are useful as inhibitors of cell-cell interactions mediated by L-selectin and P-selectin, particularly leukocyte adhesion, migration and infiltration. In addition, the compositions interact directly with HS-GAGs and are therefore useful as inhibitors of any HS-GAG mediated processes and conditions.

Due to the ability of the thieno[2,3-c]pyridine compounds to inhibit cell-matrix and cell-cell interactions, it is reasonably expected that these compositions will be useful in the treatment or prevention of diseases and

disorders related to cell adhesion and cell migration mediated by GAG-ECAM interactions, by inhibiting a cascade of events that lead to the development of said diseases and disorders.

Indeed, Example 5 in the specification discloses *in vitro* assay results obtained when inhibition of L-selectin binding to HS-GAGs was determined for the various thieno[2,3-c]pyridine inhibitors. Example 7 describes inhibition of leukocyte adhesion to endothelial cells under shear flow exhibited by these inhibitors. Examples 8-12 describe *in vivo* results obtained for several models of inflammatory diseases in mice using compositions comprising thieno[2,3-c]pyridine compounds.

Example 11 in the specification and Figs. 9 and 10 disclose *in vivo* efficacy of Compound no. 11 in TNBS-induced colitis in mice, which is a standard model for inflammatory bowel disease. The therapeutic effect of Compound no. 11 as shown in Figs. 9 and 10, was dose-dependent and statistically significant both after intra-peritoneal as well as oral administration.

Example 8 discloses that Compound no. 11 inhibited leukocyte and neutrophil infiltration into mouse peritoneum. Leukocyte and neutrophil infiltration is considered a hallmark of inflammatory bowel disease. According to Table 1 in

Example 5, which discloses results of *in vitro* inhibition of L-selectin binding to HS-GAGs, Compound no. 11 presented the lowest IC50 value of 0.35μM.

Another use of the compositions of the present invention is for treating multiple sclerosis, which is demonstrated in the description in Example 12 and Fig. 11 by *in vivo* tests results obtained in experimental autoimmune encephalomyelitis (EAE), a standard animal model of multiple sclerosis. Multiple sclerosis, as is well known, is a progressive neurological autoimmune disease that is thought to be the result of a specific autoimmune reaction in which certain leukocytes initiate the destruction of myelin, the insulating sheath covering nerve fibers. Murine monoclonal antibodies directed against L-selectin have been shown to suppress EAE (Archelos, J.J., *J. Neurol. Sci.*, 159:127-34, 1998). As shown in Fig. 11, Compound no. 11 inhibited symptoms of EAE at two concentrations tested.

Thus, the subject matter claimed in claims 42 and 43 is assessed by physiological activity, by *in vitro* and *in vivo* results that prove that compound 11 exhibits the desired pharmacological activity and that inflammatory bowel disease and multiple sclerosis are the inflammatory diseases that benefit from this activity.

To summarize, and taking into account the high level of skill in the present art and the results already demonstrated in applicants' specification, and the reasonable expectations based thereon, the rejection on the first paragraph of Section 112 should be withdrawn, and such is respectfully requested.

Claims 3-4 and 7-9 have been rejected as being anticipated by Balakin et al, 2002 ("Balakin"), which, according to the examiner, discloses one of the claimed compounds and compositions on page 1339, Figure 5, and in the abstract which discloses that the compound is useful as a drug. This rejection is respectfully traversed.

Balakin is mentioned in the background section of the present application and the compound disclosed in Balakin was originally excluded from the scope of the present invention, as stated on page 10, lines 22-26 of the applicants' specification:

> It is to be understood that the present invention does not encompass any compounds or pharmaceutical compositions thereof for which such a pharmaceutical activity has been disclosed. Explicitly excluded is the compound 2-[[4-[(1,3,3-trimethyl-6-azabicyclo[3.2.1.]oct-6-yl)sulfonyl]benzoyl]amino]-6-ethyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylic acid ethyl ester.

Thus, in fact, Balakin is not relevant to the novelty of claims 3-4 and 7-9, and does not anticipate any of these claims.

Nevertheless, in amended claims 3, 7 and 9, the definitions of the substituents R2, R3 and R4 have been amended by deleting options which cover R2 as ethoxycarbonyl, and R3 and R4 together as a 5-7 membered saturated bicyclic nitrogen containing heterocyclyl. Compounds falling under the scope of the deleted options have also been deleted in allowable claim 10.

Withdrawal of the rejection is in order and is respectfully requested.

Applicants have not received an examiner initialed copy of the listing of references cited in the Information Disclosure Statement filed October 19, 2005, and applicants accordingly request such an examiner initialed copy.

The prior art documents of record and not relied upon by the PTO have been noted, along with the implication that such documents are deemed by the PTO to be insufficiently material to warrant their application against any of applicants' claims.

Applicants believe that all issues raised in the Official Action have been addressed above in a manner that

should lead to patentability of the present application.

Favorable consideration and early formal allowance are

respectfully requested.

Respectfully submitted,

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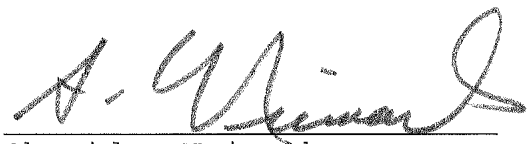
By 
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